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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/707,747	PAUL ET AL.	
	Examiner	Art Unit	
	David C. Thomas	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-36* is/are pending in the application.

4a) Of the above claim(s) *31-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's cancellation of claims 1-15 and addition of new claims 16-36 on June 5, 2006 is acknowledged. However, claims 31-36 are withdrawn as discussed below. Therefore, claims 16-30 will be examined on the merits.

Election/Restrictions

2. Newly submitted claims 31-36 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 31-36 (group II) are drawn to primer and probe sets for detecting the presence of *K. brevis*, while claims 16-30 (group I) are drawn to methods for screening a sample for the presence of *K brevis* and therefore the claim groups represent different inventions. These two groups are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the primers or probes of group II can be used for other applications besides screening a sample for the presence of a nucleic acid sequence using amplification processes, such as DNA sequencing, Southern analysis, SNP analysis, or primer extension assays.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 31-36 are withdrawn from consideration

as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 16 recites the limitation "assaying the sample for the presence of the probe". There is insufficient antecedent basis for "the probe" in this claim. For examination purposes, the phrase "assaying the sample for the presence of the probe" will be interpreted as "assaying the sample in the presence of a probe."

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being anticipated by Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Buck et al. (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

With regard to claim 16, Yoon teaches a method for screening a sample for the presence of K. *brevis,* comprising: applying an amplification process to the sample in the presence of a primer (amplification using species-specific primers, p. 11725, column 1, lines 13-24 and Table 2, supporting information), specific to a target nucleotide sequence unique to *K. brevis* (p. 11726, column 1, lines 8-14 and Figure 1A and B and GenBank Accession No. AY119786)*;* and assaying the sample in the presence of a probe (PCR products were sequenced using dye terminators as probes, p. 11725, column 1, lines 24-29).

With regard to claims 17 and 18, Yoon teaches a method wherein the target nucleotide sequence is about 87 to 91 base pairs in length and comprises the ribulose 1,5-biphosphate carboxylase-oxygenase large subunit (rbcL) of *K. brevis* (rbcL gene region is amplified, p. 11724, column 2, lines 29-32 and Table 1, supporting information; using primers rbcL64F and R-173 in Table 1, a 155-base pair target would be amplified).

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general

method of identifying a specific DNA does not make the specific DNA obvious.

Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers.

Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

8. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Bowers et al. (Appl. Environ. Microbiol. (2000) 66: 4641-4648) in view of Buck et al. (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

Yoon, in view of Buck and GenBank Accession No. AY119786, teaches the limitations of claims 16-18 as discussed above.

Yoon does not teach a method for screening a sample for the presence of *K. brevis* using a real-time reverse transcriptase polymerase chain reaction or quantitative thermocycling.

Bowers teaches a method of specifically detecting harmful algal bloom species including dinoflagellates such as *Pfiesteria* using a real-time polymerase chain reaction (p. 4643, column 1, lines 19-23). Bowers demonstrates specific detection of *Pfiesteria* species in the presence of negative control samples including other harmful dinoflagellate species such as *K. brevis* (p. 4645, column 1, line 37 to column 2, line 13 and Table 1, *Gymnodinium breve=K. brevis*).

Bowers does not teach the detection of *K. brevis* sequences by the real time polymerase chain reaction using at least one specific primer.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon and Bowers since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Bowers describes a real-time polymerase chain reaction using an internal fluorescent probe to detect harmful dinoflagellates in a rapid, homogeneous assay. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with assays based on traditional PCR methodology. Furthermore, the use of a high through-put real-time PCR assay greatly improves upon other traditional methods of processing large numbers of environmental water samples such as scanning electron microscopy

which are very labor-intensive, and also provides a method that is more easily adapted for field-based testing.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to

render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

9. Claims 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al., (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Bowers et

al., (Appl. Environ. Microbiol. (2000) 66: 4641-4648) and further in view of Buck et al (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

Yoon, in view of Buck and GenBank Accession No. AY119786, teaches the limitations of claims 16-18 and Yoon and Bowers together teach the limitations of claim 19 as discussed above, in view of Buck and GenBank Accession No. AY119786.

With regard to claims 20-23, Yoon teaches a method wherein the at least one primer comprises a nucleotide sequence selected from the group consisting of SEQ. ID. No. 1 (Table 1, supporting information, GeneBank Accession No. AY119786, positions 729-748) and SEQ. ID. No. 2 (Table 1, supporting information, GeneBank Accession No. AY119786, positions 819-798), wherein SEQ. ID. No. 1 comprises a forward primer (GeneBank Accession No. AY119786, positions 729-748) and SEQ. ID. No. 2 comprises a reverse primer (GeneBank Accession No. AY119786, positions 819-798), to generate a 91-base pair amplicon (from positions 729 to 819 of GeneBank Accession No. AY119786).

With regard to claims 24 and 25, Yoon teaches a method wherein the amplification process is applied to the sample in the presence of a probe, wherein the probe comprises a nucleotide sequence consisting of SEQ. ID. No. 3 (Table 1, supporting information, GeneBank Accession No. AY119786, positions 758-775).

Yoon does not teach a method of screening a sample for the presence of *K. brevis* using a real-time reverse transcriptase polymerase chain reaction.

Bowers teaches a method of specifically detecting harmful algal bloom species including dinoflagellates such as *Pfiesteria* using a real-time polymerase chain reaction (p. 4643, column 1, lines 19-23) and internal probes (p. 4643, column 1, lines 23-30 and p. 4645, column 1, lines 8-14). Bowers demonstrates specific detection of *Pfiesteria* species in the presence of negative control samples including other harmful dinoflagellate species such as *K. brevis* (p. 4645, column 1, line 37 to column 2, line 13 and Table 1, *Gymnodinium breve=K. brevis*).

Bowers does not teach the detection of *K. brevis* sequences by the real time polymerase chain reaction using at least one specific primer and a probe.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon and Bowers since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Bowers describes a real-time polymerase chain reaction using an internal fluorescent probe to detect harmful dinoflagellates in a rapid, homogeneous assay. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with assays based on traditional PCR methodology. Furthermore, the use of a high through-put real-time PCR assay greatly improves upon other traditional methods of processing large numbers of environmental water samples such as scanning electron microscopy which are very labor-intensive, and also provides a method that is more easily adapted for field-based testing.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

10. Claims 26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Leone et al. (Nucleic Acids Res. (1998) 26: 2150-2155) and further in view of

Buck et al (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

Yoon, in view of Buck and GenBank Accession No. AY119786, teaches the limitations of claims 16-18 as discussed above.

Yoon does not teach a method of screening a sample for the presence of *K. brevis* using nucleic acid sequence based amplification in the presence of a probe.

With regard to claims 26 and 28, Leone teaches a method of homogeneous real-time detection of RNA using nucleic acid sequence based amplification and molecular beacon probes (p. 2151, column 1, lines 6-15 and line 42 to column 2, line 12).

Leone does not teach a method of detection of *K. brevis* sequences by nucleic acid sequence based amplification using at least one specific primer and a probe.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon and Leone since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Leone teaches an alternative method of DNA detection, nucleic acid sequence-based amplification (NASBA), that can also be adapted to a real-time format, and thus is very suitable for detection of dinoflagellate species such as *K. brevis*. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with amplification assays based on traditional non-fluorescence methodologies. Because NASBA is an isothermal process that doesn't require heavy equipment such as

thermocyclers, when combined with molecular beacon probes, this method is suitable for high through-put sample analysis and the development of automated workstations, and is also easily adapted for field-based testing. Furthermore, because the method is ideally suited for amplifying RNA analytes using one reaction mixture, the application range is expanded beyond genomic targets to gene expression targets such as the mRNA product of the rbcL gene of *K. brevis*.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence

as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all

possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

11. Claims 27, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoon et al. (Proc. Natl. Acad. Sci. USA. (2002) 99: 11724-11729) in view of Leone et al. (Nucleic Acids Res. (1998) 26: 2150-2155) and further in view of Buck et al. (Biotechniques (1999) 27: 528-536) and further in view of GenBank Accession No. AY119786.

With regard to claims 27 and 30, Yoon teaches a method wherein the at least one primer comprises a nucleotide sequence selected from the group consisting of SEQ. ID. NO. 4 (Table 1, supporting information, Gene Bank Accession No. AY119786, positions 733-751) and SEQ. ID. No. 5 (Table 1, supporting information, Gene Bank Accession No. AY119786, positions 819-798, representing the 22 3-prime most bases of this NASBA primer complementary to the target; the remaining portion SEQ ID No. 5 serves as a transcription initiation sequence, see Leone, Figure 6), to generate an 87-base pair amplicon (from positions 733 to 819 of GeneBank Accession No. AY119786).

With regard to claim 29, Yoon teaches a method wherein the probe comprises a nucleotide sequence consisting of SEQ. ID. No. 3 (Table 1, supporting information, Gene Bank Accession No. AY119786, positions 758-775).

Yoon does not teach a method of screening a sample for the presence of *K. brevis* using nucleic acid sequence based amplification in the presence of a probe.

With regard to claims 27, 29, and 30, Leone teaches a method of homogeneous real-time detection of RNA using nucleic acid sequence based amplification and

molecular beacon probes (p. 2151, column 1, lines 6-15 and line 42 to column 2, line 12).

Leone does not teach a method of detection of *K. brevis* sequences by nucleic acid sequence based amplification using at least one specific primer and a probe.

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Yoon and Leone since Yoon teaches the detection of a sequence specific to *K. brevis* in the rbcL gene using a reverse-transcriptase polymerase chain reaction method, while Leone teaches an alternative method of DNA detection, nucleic acid sequence-based amplification (NASBA), that can also be adapted to a real-time format, and thus is very suitable for detection of dinoflagellate species such as *K. brevis* in water samples. Thus, an ordinary practitioner would have been motivated to combine these methods to provide a rapid test for harmful algal bloom species that results in an added level of specificity compared with amplification assays based on traditional non-fluorescence methodologies. Because NASBA is an isothermal process that doesn't require heavy equipment such as thermocyclers, when combined with molecular beacon probes, this method is suitable for high through-put sample analysis and the development of automated workstations, and is also easily adapted for field-based testing. Furthermore, because the method is ideally suited for amplifying RNA analytes using one reaction mixture, the application range is expanded beyond genomic targets to gene expression targets such as the mRNA product of the rbcL gene of *K. brevis.*

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Yoon, which are 100% derived from sequences expressly suggested by the prior art of Yoon as useful for primers for the detection *K. brevis,* and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Response to Arguments

12. Applicant's arguments filed June 5, 2006 have been fully considered but they are not persuasive.

The applicant argues that Yoon does not teach, describe or suggest a sequence unique to *K. brevis*. Yoon clearly states that species-specific primers were used in the PCR amplification of some sequences such as the *psaA* gene for some algal species, (p. 11725, column 1, lines 16-18), though general primers were used in other cases and also for the rbcL gene (Table 2). Thus, it is agreed that Yoon alone does not teach sequences specific to *K. brevis*. However, as stated above, Yoon teaches species-specific detection of some algal species, and it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to design species-specific primers based on the known sequence of the *K. brevis rbcL* gene (Gene Bank Accession No. AY119786) for the purposes of species-specific screening of samples for this organism.

Applicant argues that Yoon does not teach a method of detection of unique sequences specific to *K. brevis* in the rbcL gene from impure samples. In fact, the methods of Yoon, using RT-PCR to amplify sequences specific to some algal species, were applied to cultures obtained from various collections of algae, which initially were collected in the field (Yoon, p. 11724, column 2, line 38 to p. 11725, column 1, line 12). Though the cultures that one would purchase from such a source may or may not have represented pure cultures, those samples obtained in the field would certainly be impure and would require identification and confirmation of the species by a method such as PCR. Furthermore, testing a culture of algae is equivalent to testing a sample, whether

other species of algae or other unrelated organisms are present or not. Regardless of the purity, the PCR assays would not be useful unless the method can specifically amplify and detect the species of interest, which the method of Yoon clearly can do. Again, when combined with the known sequence of the *rbcL* gene (Gene Bank Accession No. AY119786), it is obvious the methods of Yoon can be used for detecting sequences of *K. brevis*.

Applicant then argues that none of the references, including that of Buck, teach a specific primer of which the claimed invention can be considered an equivalent. The teachings of Buck in this instance are used to establish a reasonable expectation of success when designing primers based on a known sequence, not to be used alone to establish equivalency. When considering the court decision *In re Deuel*, that suggests a prior art compound may suggest its homologs because homologs often have similar properties, the claimed primers, which represent such homologs of a known sequence (the *rbcL* gene), are prima facie obvious over Yoon, which is supported by Buck in that there is a reasonable expectation of success when designing primers in this gene that may not be identical to the claimed primers.

Applicant argues that the combined references of Yoon and Bowers, or Yoon, Bowers, Buck and GenBank Accession No. AY119786, or Yoon, Bowers and Leone, or Yoon, Bowers, Leone, Buck and GenBank Accession No. AY119786, are no longer valid 103 rejections in view of the amended claims, based primarily on the assertion that Yoon does not overcome the shortcomings of the other references to provide a species-specific method to detect *K. brevis*. As discussed above, it has been established that

Yoon, in view of Buck and GenBank Accession No. AY119786, teaches a method to detect the *rbcL* gene in *K. brevis*. Therefore, the 103 rejections are maintained for the amended claims.

Finally, applicant argues that the GenBank sequences that are homologous to the SEQ. ID. numbers are identical instead of complementary to each other. Primers are designed to hybridize to one of the two strands during PCR amplification, and rarely are both strands shown in a gene sequence. It is understood that one primer of a set binds to one strand, while the other primer will bind to the opposite strand. With regard to the argument that the *K. brevis* rcbL gene in the Genbank database may not be unique to *K. brevis*, the primer binding sequences would be expected to be unique since the primers of the invention are an exact match to the GenBank sequence. It would be expected that the sequences spanned by the amplification primers would also be unique to *K. brevis*, though flanking sequences may not necessarily be unique.

In view of the cancellation of claims 1-15, the original 112, second paragraph rejections have been withdrawn. However, a new 112, second paragraph rejection has been made in response to the newly added claims.

Summary

13. Claims 16-30 are rejected. No claims are allowable.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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